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Award Number: DAMD17-01-1-0112

TITLE: Genetic Epidemiology of Prostate Cancer

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REPORT DATE: June 2002

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	June 2002	Annual (1 June 2001 - 31 May 2002)

4. TITLE AND SUBTITLE
Genetic Epidemiology of Prostate Cancer

5. FUNDING NUNUMBER
DAMD17-01-1-0112

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 Words)*

Prostate cancer results from complex interactions among genetic, endocrine, and environmental factors. The role of testosterone and other male hormones (androgens) in the development of prostate cancer is well documented. Understanding the genetic risk factors that contribute to the occurrence of prostate cancer is crucial to the design of both preventative and therapeutic strategies, and to identify at-risk individuals. This knowledge could reduce the incidence of and death from this disease. Important factors that may result in differences in individual risk for developing prostate cancer likely include genes involved in regulation of testosterone and cell growth in the prostate. The primary objective of this grant is to investigate changes in genes that directly and indirectly regulate levels of male hormones, which in turn, affect prostate cell growth, and may ultimately cause cancer. We have begun genotyping variants in DNA samples from the 199 prostate cancer cases and 254 unaffected age-matched male population controls currently available. Genotyping is almost complete for *CYP11A1*, *CYP17*, *SRD5A2*, *IGF-1*, *IRS1*, *SHBG*, and *VDR*. Statistical methods will be used to analyze the association of these genes with occurrence of prostate cancer, age at diagnosis and disease aggressiveness.

14. SUBJECT TERMS
prostate cancer, genetics, molecular variants, genetic epidemiology

15. NUMBER OF PAGES
6

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Annual Progress Report
Grant DAMD17-01-1-0112
Period: June 1, 2001-May31, 2002

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men and the second most common cause of cancer mortality in the United States. One in five men will be diagnosed with prostate cancer over the course of a lifetime. In our aging population, research leading to a reduction in the incidence of and mortality from prostate cancer is an urgent necessity. A critical problem in prostate cancer is an understanding of risk factors involved in disease development and aggressiveness. Clinically important genetic risk factors that may result in differences in individual susceptibility to prostate cancer likely include genes involved in androgen biosynthesis, metabolism and regulation and in prostate cell growth and death. We propose to answer the following questions. What are some of the genetic risk factors that determine who develops prostate cancer? Of those individuals who develop cancer, what risk factors contribute to the age at diagnosis and to aggressiveness of the disease? Using a case-control design, we will test the hypothesis that common genetic polymorphisms (variants) in 12 genes directly and indirectly involved in altering hormonal levels and prostate cell growth are associated with prostate cancer risk. We will investigate their associations with occurrence of prostate cancer, age at diagnosis, and aggressiveness of the disease as measured by Gleason score and tumor stage-related variables.

BODY

Our progress is described by Tasks. During this past year, we obtained 199 prostate cancer cases and 254 age-matched controls. Family history, age at diagnosis, and clinical and pathological characteristics data have been obtained for the prostate cancer cases. We have begun genotyping for the genetic variants in DNA from this set of cases and controls.

Aim 1: To assay samples for the genetic variants (genotyping)

Task 1: Design allele-specific primers for genotypes to be examined on ABI. Test and optimize the genetic assays. Compare with published protocol results. Sequence to confirm that detecting the appropriate alleles. We have since purchased a real-time PCR machine and are in the process of adapting the assays to run on this machine. In the meantime, we are using the ABI for genotyping SRD5A2, VDR-polyA, IGF1, and CYP11A1 and are following published protocols for the restriction digest assays.

Task 2: Screen for variants in *IGFBP-1* to identify a variant(s) for genotyping. With the rapid pace of single nucleotide polymorphism (SNP) discovery, we decided to do an *in silico* search instead of screening for variants by sequencing. To perform this search, we looked for variants in IGFBP1

identified in public databases. Two polymorphic SNPs in the coding region, I253M and V183I, that may change function have been identified and will be genotyped as part of Task 5.

Task 3: Identify male controls which match prostate cancer cases. For the 199 prostate cancer cases for whom we have DNA, diagnosis and follow-up data, we have identified 254 age-matched male population-based controls.

Task 4: Aliquot DNA from all samples available. DNA has been diluted to 10 ng/ul and placed into racks of 96 tubes for multi-channel pipetting. This includes the 199 prostate cancer cases and 254 age-matched controls.

Task 5: Perform genotyping on the 800 DNA samples for the 18 assays in 12 genes. We have completed genotyping on the 199 prostate cancer cases for *CYP17, IGF-1, CYP11A, VDR-BsmI, VDR-TaqI, VDR-polyA, IRS1, SHBG,* and *SRD5A2-str*. For the 254 controls, we are in the process of completing genotyping on the variants that have been examined in the cases.

Task 6: Read genotypes and enter into our Sybase database. Genotypes that have been completed are currently entered in an excel spreadsheets. The genotypes are assigned by 1 lab specialist and entered into the database. A second lab specialist then rereads the gels and checks that the data entry was correct.

Aim 2: To statistically analyze the association of genes assayed in Aim 1 with prostate cancer age at diagnosis and aggressiveness, as measured by Gleason score and tumor stage-related variables. Aim 3: To statistically analyze the association of genes assayed from Aim 1 with occurrence of prostate cancer.

Task 7: Design data entry forms for entering data into Sybase. This task is completed so that we can download the data into Sybase.

Task 8: Edit data. Add data from medical records and Utah Cancer Registry. The prostate cancer cases were diagnosed from 1992-2000. Age at diagnosis ranged from 45-78 years with a mean age of 62.6 years and a median age of 63 years. Of the tumors, 10 were well-differentiated, 139 were moderately differentiated and 50 were poorly differentiated. Thirteen of the cases had another type of cancer, either previous to or after diagnosis of prostate cancer. We obtained follow-up data on these cases with the dates of last follow-up ranging from 2000-2002. These data are in the excel spreadsheet with the genotypes. Of the 199 prostate cancer cases, 15 are now deceased including 1 case diagnosed at 49 years of age who died from metastatic prostate cancer.

Task 9: Months 25-27: Test models and analysis methodologies.
Task 10: Months 26-36: Perform statistical analyses as outlined in Methods.
Task 11: Months 34-36: Prepare and submit final report and manuscripts.
Tasks 9, 10, and 11 have not yet begun.

KEY RESEARCH ACCOMPLISHMENTS:

- Collection of family history, age at diagnosis, and clinical and pathological characteristics data on 199 prostate cancer cases.
- Identification of coding variants in IGFBP-1
- Genotyping almost complete for 199 prostate cancer cases and 254 age-matched controls for 9 variants in 7 genes.

REPORTABLE OUTCOMES: There are no outcomes yet to report. We are in the process of generating the data to be analyzed.

CONCLUSIONS: There are no conclusions at this time as we are just in the data-gathering stage of this project. During this next year, we will perform preliminary statistical analyses of the data to determine if there any indications that these variants are associated with prostate cancer risk.

REFERENCES: None

APPENDICES: None